AMENDMENTS TO THE SPECIFICATION

Please insert the following paragraphs [0032a] through [0032c] after paragraph [0032]:

[0032a] For example, Narendran, in discussing the use of olanzapine to treat psychotic mood disorders cites that "preliminary data on olanzapine in patients with schizophrenia, schizophreniform disorder, and schizoaffective disorders suggested that his drug may posses acute antimanic and antidepressant properties in addition to its antipsychotic proprieties." Several studies indicating the efficacy of olanzapine were described:

> Baker et al. reported that patients with schizophrenia treated with 10 mg/day of olanzapine were noted to have a significant reduction in Hamilton Rating Scale for Depression scores in comparison with those receiving olanzapine, 1 mg/day, or placebo. Tollefson et al. examined the efficacy of olanzapine in treating depressive signs and symptoms associated with schizophrenia and schizoaffecive and schizophreniform disorders in a 6-week double-blind, placebo-controlled trial. Olanzapine was found to be statistically superior to haloperidol in baseline to endpoint changes as measured by the Montgomery-Asberg Depression Rating Scale (MADRS) total score (6-point decline compared with a 3-point decline with haloperidol, p=.001). The authors concluded that olanzapine had a direct therapeutic effect on the depressive signs and symptoms after covarying for indirect effects, including positive, negative, and extrapyramidal symptoms via a linear regression "path analysis." For that trial, a recent subanalysis of schizoaffective disorder, bipolar type patients was reported. In the schizoaffective patients who were currently depressed, olanzapine was noted to be superior to haloperidol in the reduction of the MADRS scores (p=.002). In the schizoaffective patients who were currently manic, olanzapine was as effective as haloperidol in decreasing the Brief Psychiatric Rating Scale (BPRS) mania score (p=.25). (The BPRS mania score was derived by adding the BPRS items assessing conceptual disorganization, grandiosity, hostility, excitement, and disorientation.) In a retrospective naturalistic study of 150 consecutively admitted inpatients with a diagnosis of psychotic disorders treated with olanzapine, Zarate et al. reported an overall response rate of 62% for all patients and a statistically significant better response rate of 83% for the bipolar disorder patients. In a blinded chart review study of the treatment of 30 inpatients with psychotic depression. Rothschild and colleagues reported a response rate of 67% among patients treated with olanzapine compared with 27% in age- and sex-matched patients treated with typical antipsychotics.

[0032b] (Narendran *J. Clin. Psychiatry* 2001 at 510; internal references omitted). In the original study conducted by Narendran by reviewing hospital records and by follow-up interviews, Narendran concluded:

> Both the psychotic mood disorders patients (N=32) and the schizophrenic patients (N=18) who continued to be treated with olanzapine showed a statistically significant change toward improvement on the CGI and GAF-EQ during the course of this study (Table 3). Although the psychotic mood disorders cohort exhibited a greater change from baseline to follow-up on the CGI compared with the schizophrenic cohort, this difference between groups failed to reach statistical significance. Seventy-five percent (24/32) of the psychotic mood disorders patient group and 100% (18/18) of the schizophrenic patients taking olanzapine remained hospitalized at follow-up.
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> A subanalysis was performed on the individual subscale scores of the K Axis V before and after treatment with olanzapine after lowering the a value of significance utilizing the Bonferroni correction (Table 4). The psychotic mood disorders group revealed a statistically significant change from baseline to follow-up scores in the psychological impairment, violence, and social skills subscales in contrast to the schizophrenic group, which revealed a significant change in score only on the violence subscale.

Id. At 512.

[0032c] Guille also conducted a review of medical records in patients with bipolar disorder who received at least one dose of olanzapine. The mean dosage was 11.7 ± 6.2 mg/day. Guille found that

> in a 49-week open-label extension of a clinical trial of olanzapine for acute mania, 113 bipolar type I patients were followed for an average of 6.7 months while taking a mean dose of 13.8 mg/day of olanzapine. YMRS scores improved from 25.5 at baseline to 7.5 on follow-up ($p<.001$), and HAM-D scores improved from 12.2 to 6.5 ($p<.001$). Few EPS were noted. Adjunctive lithium was allowed, although the available abstract is unclear about how many patients received lithium.

Guille et al. *J. Clin. Psychiatry* 2000 at 640.

Please amend paragraph [0033] as follows:

[0033] Olanzapine has also been shown to be an effective therapy for the treatment of psychosis among patients with Alzheimer's disease (AD). (WS Clark *J. Clin. Psychiatry* 2001; Vol. 62: 34-40, which is incorporated by reference herein in its entirety, and references cited therein.) This study shows that, in patients with possible AD with concurrent agitation/aggression and no or minimal hallucinations and/or delusions, olanzapine treatment results in an overall significantly

lower emergence of psychotic symptoms compared to placebo. For example, Clark studied a group of nursing home patients and found that:

> The results of these post hoc analyses indicate that, overall, olanzapine was effective in decreasing the emergence of psychotic symptoms in patients with AD who were relatively free of these symptoms at baseline. Previous studies have demonstrated that olanzapine is effective in reducing psychotic symptoms in schizophrenia, acute mania, and AD. Moreover, in a recent report, olanzapine was shown to prevent relapse of psychosis in stable schizophrenic patients, suggesting it may have a prophylactic effect as well as an ameliorative effect on psychosis. This is study is the first to suggest that olanzapine may effectively attenuate the emergence of acute psychosis in patients with AD.
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> The effect pattern seen here for the 3 doses of olanzapine was not consistent with the efficacy results in the overall study. The parent study found the 5-mg/day dose to be not only the most efficacious in reducing psychotic symptoms but also the safest. The 10-mg/day dose also demonstrated significant efficacy for olanzapine relative to placebo, but the results were less rebust. The 15-mg/day dose group failed to separate from the placebo group in their expression of psychotic symptoms and had a less tolerated safety profile. In contrast, the results here indicate attenuation of the emergence of psychosis across the 3 olanzapine doses, with a tendency toward greater effects at the higher doses. The sample size and short duration of this study are limitations that do not allow powerful comparisons among olanzapine doses. Given the safety and efficacy results from the parent study in combination with the findings here, 5 mg/day of olanzapine would be the most appropriate target does for further study on reducing the emergence of psychosis in dementia.

Clark *J. Clin. Psychiatry* 2001 at 38-39.

[0033a] Further, olanzapine has demonstrated efficacy in patients with Acute Mania. (M Tohen *Am. J. Psychiatry* 1999 Vol. 156: 702-709, which is incorporated by reference herein in its entirety.) Tohen conducted a randomized, placebo-controlled, double-blind study of pateients between 18 and 65 years of age. Dosages were in the range of 5-20 mg/day, adjust individually after an initial treatment with 10 mg/day. Tohen found:

> This suggests that olanzapine is effective in the treatment of acute mania, as evidenced by the decreases in total scores on the Young Mania Rating Scale; in severity of mania ratings on the CGI, Bipolar Version; and in total and positive symptom scores on the Positive and Negative Syndrome Scale. Also, the percentage of patients who discontinued treatment because of lack of efficacy was significantly smaller (p=0.02) in the olanzapine group (28.6%) than in the placebo group (47.8%). That olanzapine may have antimaine effects is further suggested by the magnitude of response to treatment as illustrated by the responder analysis, where 48.6% of the olanzapine-treated patients had an improvement of

50% or more in Young Mania Rating Scale total score, compared with 24.2% of the placebo-treated patients.

Tohen *Am. J. Psychiatry* 1999 at 706.